AMERICAN JOURNAL OF PHARMACY

★ AND THE SCIENCES SUPPORTING PUBLIC HEALTH ★

DR. LLOYD E. BLAUCH
Chief for Education in the Health Professions,
U. S. Office of Education

(See p. 222 for Dr. Blauch's article on pharmaceutical education)

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Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

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Vol. 125 JULY 1953 No. 7

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EDITORIAL

THE PHARMACEUTICAL CURRICULUM

IN this issue of the Journal we have published the scholarly address given by Dr. Lloyd E. Blauch at the Rutgers' Pharmaceutical conference held in May. Dr. Blauch is Chief for Education in the Health Professions of the Office of Education of the Department of Health, Education and Welfare, Washington, D. C. For many years Dr. Blauch has been a specialist in the field of higher education. He was closely affiliated with the work of the Pharmaceutical Survey serving as the Assistant Director in charge of curriculum studies. Together with Dr. George Webster of the University of Illinois, he prepared the book recently released, "The Pharmaceutical Curriculum." As might be expected by one who knows these distinguished educators this book is a fine example of careful analysis, logical conclusions and forthright recommendations.

Our readers are urged to read Dr. Blauch's address in this issue. Barely has there been a better opportunity to read a dissertation on this subject by one who is unbiased, disinterested, and fully qualified as an expert in education and curriculum planning.

In developing his theme Dr. Blauch has not made the all too common error of deciding in advance what time should be required to train a pharmacist and then producing a theme to prove his point. He has by inquiry and careful study analyzed what training the future pharmacist needs and then determined what courses are required to give this training. In other words he is suggesting that the shoe fit the foot rather than the reverse.

There has been much debate and considerable heat concerning the future of the pharmaceutical curriculum. Without attempting to delve into the finer points of the debate, this editor wishes to record his personal views on two aspects of the problem not usually appreciated by those who are opposed to any drastic change in the pattern of pharmaceutical education.

In the first place, the student entering college today will be at the prime of his professional career about 1980 and, in most instances,

will still be in practice the year 2000. For too many pharmacists fail to realize that what is seemingly enough training for today may fall woefully short of the needs of the year 2000. It must be remembered that there is an unavoidable and considerable lag between the program given in college and its full impact on the profession. For example, we have had a mandatory 4 year course for over 15 years and yet there are still many more pharmacists in practice who had a 2 or 3 year course than there are those who have had the 4 year course. Can we be sure that today's training will fully meet the needs thirty or forty years hence? If not, now not then, is the time to act.

Another factor, and a most important one, is the challenge posed by the rapidly changing pattern of medical care and pharmacy's position in the scheme of things. There are many in our profession who labor under the false concept that by opposing change it can be prevented or at least indefinitely postponed.

All of us can see in just the last decade tremendous changes in pharmaceutical practice. That still further changes will occur, just as profound, is certain. If pharmacy is to maintain its position let alone better it, pharmacists must be prepared to meet the challenge. Some would have us do this by a policy of containment, i.e., let the changes occur and then try by emergency measures to meet them. Such a policy is fatal for it offers "too little and too late." Others, as Dr. Blauch, would have us anticipate our problems and prepare to meet them. This is the pathway of wise educational statesmanship.

About fifty years ago this country was dotted with carriage makers. They were highly skilled and proud craftsmen and their product was in great demand. The advent of the "horseless carriage" was scorned by most who swore never to have anything to do with such noisy and odorous contraptions. A few far-sighted carriage makers rather than resisting change met it and became a part of it. Those who opposed it are long since forgotten and their fine carriages are seen only in museums. Those who with vision learned about motors, fuels and "gadgets" are today the great names of automotive history.

Pharmacy, today, has a challenge will we meet it with vision and in time?

PHARMACEUTICAL EDUCATION AND ITS ADEQUACY, OR INADEQUACY, IN PREPARING THE GRADUATES FOR THE MANY DIVERSIFIED CAREERS IN PHARMACY *

By Lloyd E. Blauch **

I ASSUME that the great majority of you are engaged in some way in the practice of pharmacy. It seems appropriate, therefore, for me to begin this address with the statement that pharmaceutical education should be of great concern to you. For this there are several reasons.

It is only natural that you should be concerned about those who will soon be your competitors and later your successors. The newcomers to a profession, if they are competent and high minded, help to create a professional atmosphere in which the highest standards of public service may prevail, but those who are incompetent and low minded tend to demoralize a profession and degrade its standards of service. Being men who, I am sure, are proud of your profession, you have a desire to leave it to able and worthy successors who will make it a finer and better profession. Unquestionably this matter is of more than passing moment to you.

The colleges of pharmacy are the gateway to the profession. Today there is no other way for men and women to become pharmacists than to pass through one of those institutions. Thus the colleges are in a strategic position which is often overlooked by members of the profession. By admitting, screening, and graduating students the colleges, to a very large extent, decide how many pharmacists the country will have, what kind of persons they will be, and what will be their intellectual, civic, and professional accomplishments. To be sure, other factors besides the instruction of the colleges of pharmacy help to determine the character of the pharmaceutical profession, but the colleges exert a tremendous influence. Therefore it behooves the profession to take a deep interest in its schools.

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* Address to the Second Annual Rutgers Pharmaceutical Conference Rutgers University, May 13, 1953.

** Chief for Education in the Health Professions, Office of Education, Department of Health, Education, and Welfare, Washington, D. C.

In dealing with this subject of pharmaceutical education I propose *first* to refer to the varied professional services of pharmacists, *second* to describe professional education in pharmacy, and *lastly* to make some evaluation of the program of pharmaceutical education. In doing this I shall use many statements from the book entitled *The Pharmaceutical Curriculum* published last year.[1]

Varied Services of Pharmacists

When one mentions the profession of pharmacy he usually has in mind the operator in a retail establishment that dispenses drugs, for the great majority of pharmacists render a very large part of their professional service in that way. In this capacity the pharmacist is required to engage in two groups of activities. *First,* he has to recognize, identify, select, procure, create, process, standardize, stabilize, fabricate, test, evaluate, and preserve all substances of whatever kind and combination used in preventive and curative medicine. In recent years the development of large-scale scientifically controlled production of medicinals has brought significant changes in these activities in the retail pharmacy, with the result that today no one pharmacist engages in all of them. Nevertheless, every pharmacist has to do in one way or another with most of them.

The second group of activities of the retail pharmacist consists of distributing medicinal substances to members of the other health professions and the public. This is done partly through the compounding and dispensing of the physicians' prescriptions. The compounding of a prescription is, of course, an activity which entails serious professional responsibility.

I believe it is not enough that a pharmacist can read and fill the prescription he receives. In the interest of the patient he should be able to adopt a critical attitude toward the mixtures he prepares, with respect to their therapeutic application. I am not suggesting, of course, that the pharmacist should usurp the professional function of the physician. Far from it. However, he may be of great help to the physician if, as occasion warrants or merits, he can and does point out relative advantages and disadvantages among therapeutic agents and thus indicates to the physician wherein he may improve his prescribing. Indeed the physician, having made a diagnosis, should

1. Lloyd E. Blauch and George L. Webster, *The Pharmaceutical Curriculum.* Washington, D. C., The American Council on Education, 1952.

find it possible with complete confidence to call upon the pharmacist for advice as to the best available agent or agents for the treatment.

It is frequently said that most of the prescriptions given by physicians are for medicinals that have been prepared in manufacturing establishments. Such prescriptions do not require the pharmacist to compound a mixture. It must be said, however, that about one-fourth of the perscriptions do require compounding, which means that this form of pharmaceutical service is still of sizable proportion and great significance. Obviously no one could possibly be a pharmacist who could not compound prescriptions.

I have referred to the development of large-scale production of medicinals as having changed somewhat the activities of the retail pharmacist. It has at the same time enlarged his professional responsibility because now he has to handle and become familiar with an ever increasing number of new diagnostic and therapeutic agents, many of which require comprehensive scientific and technical knowledge on his part. Thus he has become increasingly a scientific purveyor of manufactured medicinals and a technical adviser regarding their use.

With the rapid multiplication of drugs produced by the pharmaceutical industry the services of the well educated pharmacist are, more than ever before, needed by the other health professions and the public. So extensive is the knowledge and effort required to know the various drugs and their uses that it becomes well-nigh impossible for anyone but the pharmacist to keep completely up to date in this field. He can perform a particularly useful service in advising on competing drugs for which conflicting claims are made. The great increase in other products than drugs, such as rodenticides, parasiticides, and fungicides, on which the pharmacist can give sound advice, makes his service increasingly valuable to the public.

Records kept by pharmacists of questions asked them by physicians, other professional personnel, and laymen bear witness to the fact that these groups rely upon the pharmacist for a surprisingly large amount of information and advice. Apparently he is expected to know everything about drugs *or* to be able to find the answer to just about any question concerning them.

So far this paper has been concerned primarily with the scientific and technological activities of the pharmacist in the retail pharmacy. Another aspect of his work relates to the management of his establishment so that it will remain solvent and yield for him a sufficient finan-

cial return for his livelihood and professional improvement and the support of his family. This part of his work may become a hazard to the professional side of his activities; he has to conduct it in such a way as to conserve the professional aspects of the service he renders.

One development which is having an impact on pharmacy is the great increase in public and private hospitals and the establishment of pharmacies in a considerable number of them. It is estimated that about 3,500 registered pharmacists are engaged in such pharmacies. These pharmacists are in very strategic positions to render professional service. Their daily contact wtih physicians provides for them unequalled opportunities to give professional assistance and to furnish unbiased information concerning drugs and drug preparations.

This statement concerning the activities of pharmacists would not be complete without mentioning a number of others, mostly outside retail and hospital pharmacies. In pharmacy, as in all fields of applied science, there is increasing demand for persons who can carry on research. Much of this work is done in manufacturing establishments, and a sizable amount of it is also carried on in the colleges of pharmacy, particularly those that offer graduate work. The Federal Government today supports a large amount of research in drugs, some of it on contract with institutions of higher education and research laboratories. It is generally reported that there are not available enough trained persons to do the research for which funds are becoming available.

An increasing number of pharmacists are required by the Government. The Army, the Navy, the Public Health Service, the Veterans Administration, and the Food and Drug Administration employ pharmacists in some capacity or other. Although the number who are so engaged is not large, these positions provide unique opportunities for professionally trained personnel and they call for training of a high order.

The development of pharmaceutical education to the point where it is a member of the university family has created a need for a sizable number of teachers who are well trained in pharmaceutical subjects, usually to the point where they have obtained graduate degrees. In pharmacy, as in other professional fields, there is a shortage of well prepared teachers. This situation exists partly because the professional colleges do not give sufficient attention to the preparation of teachers. Usually the colleges devote their energy to preparing men and women for the practice of the profession, particularly in the retail

pharmacy, almost entirely to the neglect of stimulating upperclassmen to prepare for teaching. The result is that not enough talented students seriously consider teaching as a career.

The development of pharmacy as a profession has made necessary a group of miscellaneous activities which are carried on by men and women who are professionally trained. A small number of pharmacists, some on a full-time basis, others on a part-time basis, edit and manage the numerous pharmaceutical journals. Another group manage the activities of the various organizations of the profession. Still another group serve on the State boards of pharmacy, in which capacity they enforce the practice acts and license applicants for the practice of the profession. Although the number who are engaged in these miscellaneous activities is not large, these pharmacists perform significant professional functions which require special competence. Ability to carry them on is developed partly through the general education of the students and partly through their professional education.

I realize that in listing and describing the activities of pharmacists I have said little or nothing that you have not already known, but I recognize that, if there is to be a meeting of minds on what is to be said later, we must have some agreement and common understanding as to the functions and activities of the profession.

Professional Education in Pharmacy

In the light of the things the pharmacist is called upon to do we may now proceed to consider the nature and extent of his professional preparation. I believe it is clear that pharmaceutical education must be based on the broad proposition that pharmacy is a health profession; this must be the guiding principle in the pharmaceutical curriculum. Moreover, pharmaceutical education must be broad enough to cover preparation for the wide range of activities in the field of pharmacy. For some of these activities the undergraduate professional curriculum should provide a fairly complete preparation; for others it should afford a substantial initial preparation which can be further developed through advanced and specialized education.

What are the disciplines or fields of study which the student of pharmacy is called upon to learn? *First*, there are the physical sciences. The pharmacist's concern with substances of many kinds employed in health services makes it necessary that he have extensive

knowledge of chemistry and some understanding of physics and mathematics. In order to handle the substances properly, he must be fully conversant with their chemical and physical properties and reactions. No one can develop the ability to deal with the substances merely through repetition of routine operations and memorization of formulas and standardized operations; it can come only as he is well grounded in the physical sciences.

Second, there are the biological sciences. The ultimate purpose of the drugs the pharmacist handles is to modify, accelerate, decelerate, or inhibit the functioning of a cell, a tissue, an organ, or an organism. In order that he may intelligently and helpfully supply the materials to do this it is essential that he know something about the physiology of cells, tissues, organs, and organisms, how this is modified by malnutrition or disease, and how it responds to drugs. Because it is the responsibility of the pharmacist to prepare dosage forms of medication which will most effectively present the medicinal agent, it becomes his responsibility to know the pathways by which drugs may be administered and the dosage form of each drug which is most suitable for each pathway. Such knowledge calls for a substantial study of botany, zoology, pharmacognosy, anatomy, microbiology, physiology, biochemistry, and pharmacology.

Let me make an observation here that applies to the foundation in the sciences which the student should acquire. In a world of rapid change and a tremendous increase of knowledge, it is essential that a professional man continue his education as long as he remains active in his profession. The basis for such continuing education of the pharmacist rests primarily upon his knowledge of the physical and biological sciences. Only as he understands them is he in a position to comprehend the new discoveries in science and the new technological procedures that are invented. His mastery of science is therefore the most important educational accomplishment of the student of pharmacy.

Third, the student has to acquire certain pharmaceutical techniques which he must perform with skill and dispatch. Underlying these techniques is a vast body of factual information that must be well learned and instantly available to him. Some of the information is derived from the physical and biological sciences and some of it has been evolved by pharmacists in their study and practice. Recent research and the application of more advanced principles of physics

and chemistry are making it possible to provide greatly improved training in pharmacy. All of this comes to a head in the courses in dispensing.

Fourth, the student who is preparing to become a retail pharmacist has to acquire substantial understanding of certain phases of economics and of organization and management. So great are the financial risks involved in establishing or acquiring and operating a pharmacy and so difficult are many of the problems that have to be dealt with in such a venture that only the unwary and the reckless enter upon it without first having acquired a knowledge of administration principles through careful study and some firsthand contact. Therefore, the colleges of pharmacy have an obligation to provide their students with necessary training in this field. A mere smattering of knowledge about the administrative aspects of pharmacy is not sufficient for the pharmacist. He needs to acquire a knowledge of economic institutions, the flow of goods from producer to consumer, the management of an enterprise or establishment, the legal aspects of establishing and operating a pharmacy, and the public relations of the pharmacy and the pharmacist. This field should have the same kind of careful study as other divisions of the curriculum.

There is a *fifth* group of subjects that should also have a place in the pharmaceutical curriculum. For want of a better term they may be called professional orientation. I refer to such subjects as public health, professional communications, and the history of pharmacy. They provide certain backgrounds of information required for understanding the profession, they create an awareness of various professional relationships, and they develop certain professional attitudes and ideals.

Something should be said about the quality of the teaching and learning of these five groups of subjects. Certainly nothing less than reasonable mastery can suffice. These subjects are studied not merely to make passing grades; the knowledge and skill they afford become the foundation of professional service. The usual high university standards should prevail. It should also be said that the courses should be of such quality that graduate schools will be willing to accept them as providing an adequate foundation for graduate study.

I want now to speak briefly of a *sixth* group of studies that should enter into the education of the pharmacist, that is, subjects that prepare him to discharge his civic and social responsibilities and help

him to live a balanced and satisfying personal life. The need for attention to these matters seems so apparent that it should require no argument. More and more we are coming to demand that our professional men shall concern themselves with the broad problems of our times. Indeed, we are realizing that our educated citizens, and that means largely our professional people, must take an intelligent interest in the great social, political, and moral questions of our times if we are to survive as a people and a Nation in these troubled years. As human relations have become more complex there has arisen a demand that the men and women whom we educate shall assume larger responsibility for the general welfare. The universities in particular, which usually take a broad view of their social responsibilities, are more and more demanding that their graduates shall have some understanding of the problems of a democratic society and shall be prepared to make such contributions to the solution of those problems as befit educated men and women. To an increasing extent they are determined that they will not provide specialized training to the neglect of education in these broader phases of our life.

Leaders of the professions are likewise conscious of the fact that technical training alone is not sufficient for the practice of a profession in the modern world. They state that in many ways professional competence depends about as much on understanding the ways of men and the world as it does on technical skill. They think that, if a man is a specialist, it is most desirable that he should also be civilized, that he should be reasonable and see things in their proper perspective, that he should be capable of judging and acting wisely concerning the great and extensive interests of his community, his country, and the world in which he has his home.

Let us pursue this matter a step farther. One of the most important things about any man, a professional man as well as any other, is his philosophy of life, his outlook on the world in which he lives. It is most distressing at times to find men whose outlook has not matured along with their technical ability. Intellectually and philosophically they have not grown up. Some of the keenest observers and students of our life continue to point out that in our programs of professional and specialized education we are producing men who are more learned than ever before, but at the same time more uncultured; that we are training men in the sciences and technologies but leaving them ignorant of the essential system of ideas concerning the world and man.

All of this leads me to say that pharmaceutical education will make a very great mistake if it does not make certain that its graduates shall achieve reasonable competence in the branches of learning which aim at: (a) developing those qualities of mind and character that men have found good in governing their lives, (b) providing a basis for enjoying the rich cultural heritage of modern life, (c) making students broadminded and adaptable in their social relations, and (d) assuring a foundation for dealing rationally with the increasingly complex problems of our times.

Occasionally we hear these educational objectives referred to as mere frills and extra embellishments. They are nothing of the sort. They are a means which are intended to prepare men and women to grapple with a tough world. They should be regarded as a support of sound professional training, as a mainstay in the lives of those who render professional services to society, as a means whereby our democracy acquires strength to deal with its problems in a modern age.

I have referred to six phases of study and accomplishment that enter into the making of a pharmacist—physical sciences and mathematics, biological sciences, pharmaceutical techniques, pharmacy administration, professional orientation, and general education with reference to his personal and civic life. Taken together, they suggest what I believe is a sound philosophy of pharmaceutical education for the days ahead. How does pharmaceutical education currently stand when measured by this philosophy? Let me attempt a brief answer.

Evaluation of Pharmaceutical Education

In the short time at our disposal we cannot attempt an extensive evaluation of pharmaceutical education. It seems best, therefore, to limit the statement to what seem to me to be three outstanding weaknesses in the program. These weaknesses are, of course, more pronounced in some colleges than in others.

The *first* of them is found in the inadequate attention that is given to the biological sciences, especially in the fields of biochemistry and pharmacology. At last report, fewer than one-third of the colleges included biochemistry in their curriculums. While all the colleges provide instruction in pharmacology, much of it appears to be far below what is required for adequately training pharmacists. Few

curriculums in pharmacy provide sufficient instruction in anatomy, physiology, and biochemistry as a foundation for the study of pharmacology. This seems to me to be a serious lack. Without such knowledge the pharmacist can have little understanding of the action of the medicinals he dispenses and he can certainly not be of maximum assistance to physicians and other health personnel who seek his advice concerning those substances.

The *second* weakness I note is inadequate attention to the field of pharmacy administration. When we prepared the report on the pharmaceutical curriculum we found that about half of the colleges of pharmacy devoted to these subjects less than nine semester hours out of a total of 130. In many instances the instruction consisted only of some general economics and a few hours of pharmaceutical law.

Instruction in pharmacology and in pharmacy administration is limited by the lack of available qualified teachers—a factor which will delay improvement for some time.

The *third* weakness of pharmaceutical education is in the place it accords to the humanistic and social studies. By these I mean such subjects as history, English, government, psychology, sociology, fine arts, and philosophy. The result is a lopsided education which largely omits those things that help to make a professional man an educated man, a man of broad intellectual interests, wide human sympathy, refined taste, and deep concern with the affairs and problems of contemporary life.

Several factors are largely responsible for these weaknesses. The lack of qualified teachers in two fields has been mentioned. Inadequate financial support is another factor in some colleges. But the most obvious and widespread cause of these weaknesses is the insufficient amount of time devoted to pharmaceutical education in the majority of the colleges. I am convinced that it will not be possible to overcome these weaknesses until the entrance requirements to the colleges of pharmacy are raised to include one or preferably two years of study in a college of arts and sciences. There is a definite trend in this direction in all fields of professional education, and particularly in the health professions. There are many good reasons for it, which need not be stated here. Pharmaceutical education is clearly moving in this direction.

In Conclusion

In recent years pharmaceutical education has taken steps to improve its status and service. The Pharmaceutical Survey has presented an extensive body of information, never before available, which establishes a foundation for constructive thinking and action. The American Foundation for Pharmaceutical Education is proving most helpful in providing financial support for graduate study and for seminars aimed at improving teaching in the colleges. The American Council on Pharmaceutical Education is rendering a most useful service in developing, interpreting, and enforcing standards. And the American Association of Colleges of Pharmacy constitutes a forum for the discussion of educational questions that is resulting in better educational programs.

To be sure some retarding influences are at work in this matter. They are not new in the history of pharmaceutical education. Every advance during the past half century was marked by opposition, sometimes by those who were so constituted as to be content with things as they were, at times by others who were fearful of the consequences that higher educational standards might have on them, and at times by some who feared the profession would not support improved education.

In conclusion, I am moved to say that pharmacists, like members of other professions, take pride in their achievements and service, and surely in this dynamic world they do not want to see their professional education stand still. That would be a betrayal of the creative minds that have made the profession and brought it to the present state of accomplishment and public esteem. Pharmaceutical education must and will go forward, and you must help it to do so.

TESTING OF SOME SPECIES OF PHYTOPHTHORA FOR ANTIBACTERIAL ACTIVITY *

By Robert M. Pennington **, Charles C. Woodward **, and Henry M. Burlage ***

ALTHOUGH systematic investigations into the production of antibacterial agents by microorganisms have developed mainly since the discovery of penicillin, microbial antagonists were recognized by early investigators. Pasteur and Joubert (1877) were the first to give a clear description of bacterial antagonism, when they reported that the growth of anthrax bacilli was inhibited by an aerobic organism. Experiments by other investigators of this same period contributed to the understanding of microbial antagonism, so that by 1890 suitable bacteriological techniques for the search for antagonists had been developed. These first methods of investigation differ only slightly from those used at the present time (1).

Antagonistic properties of fungi were observed in 1892 by Reinhardt who examined reactions of various fungi when grown together. The first crystalline antibiotic, a phenolic substance produced by a species of *Penicillium*, was isolated by Gosio in 1896. He demonstrated its inhibitory action upon *Bacillus anthracis* (1, 2).

Since the time of these early discoveries, a great deal of attention has been focused on the phenomenon of microbial antagonism among the fungi. Systematic studies have shown that a large number of fungi produce antibiotic substances. Some of these substances have been studied in detail, including the most important antibiotics known today.

Extensive investigations have shown that a large number of antagonistic forms are included in two genera, Penicillium and Aspergillus. A number of antibiotic producing organisms have been found among the Basidiomycetes, but very few among the Phycomycetes.

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* These studies were made possible by a grant from Eli Lilly and Company.

** Research Scientist.

*** Dean, College of Pharmacy, University of Texas, Austin 5, Texas.

Schatz, Magnuson, Waksman, and Eagle reported that a lipid-like substance produced by a species of Phycomyces killed *Trypanosoma equiperdum* in vitro but not in vivo. This substance had little effect on *Escherichia coli, Bacillus subtilis, Bacillus mycoides,* and *Sarcina lutea* (3).

During the past several years, the College of Pharmacy in cooperation with the Biochemical Institute of the University of Texas has conducted researches aimed toward the isolation of substances from plant and other natural sources and which might have antibacterial, antiviral, and anticarcinogenic properties (4, 5, 6, 7).

Therefore, the purpose of the following experiments was to study the possibility of *Phytophthora* sp. to produce or to yield a substance or substances capable of inhibiting the growth of bacteria and, if present, what effect might it have also on tumor growth.

Experimental

Four cultures of the following were obtained from the American Type Culture Collection:

1. *Phytophthora cactorum* (10091)
2. *Phytophthora cactorum* (6419)
3. *Phytophthora fragariae* (10394)
4. *Phytophthora infestans* (9901)

and stock cultures of these were carried on the following medium:

Quaker oats	30 Gm.
Agar (Difco)	8.5 Gm.
Neopetone (Difco)	8.0 Gm.
Distilled water	500 ml

The above ingredients were mixed and then slowly boiled for fifteen minutes. The medium was dispensed in test tubes, plugged, and autoclaved at fifteen pounds and 250° F. for fifteen minutes. The tubes were slanted and stored in a refrigerator until needed.

After considerable experimentation with different combinations of ingredients a satisfactory medium was obtained for growing *P. cactorum* (6419) and (10091) in quantity.

Medium A

Bacto beef extract	3 Gm.
Bacto tryptose	10 Gm.
Bacto dextrose	5 Gm.
Sodium chloride	5 Gm.
Distilled water	1 L.

The medium was boiled slowly for fifteen minutes, dispensed in flasks of 600 milliliters capacity (100 ml. per flask), plugged, and autoclaved at fifteen pounds and 250° F. for fifteen minutes. The flasks were allowed to cool and then inoculated.

After inoculation the flasks were placed in an incubation room (24 ± 30° C.) and allowed to incubate for fourteen days and then they were filtered. The filtrate was collected and the mycelium was freeze-dried and stored for future use. The antibiotic activity of the filtrate was then tested.

Medium B *

This medium was a satisfactory one for all species grown. *P. cactorum* grows very well on it; and *P. fragariae* and *P. infestans*, which are more fastidious, grew well on the same medium when the incubation period had been extended from fourteen to twenty-four days for the maximum growth. Medium B contains the following ingredients:

Starch	2.5 Gm.
Soy bean meal	2.5 Gm.
Yeast (2019)	0.25 Gm.
Sodium chloride	0.40 Gm.
Calcium carbonate	0.50 Gm.
Ammonium sulfate	0.40 Gm.
Potassium dihydrogen phosphate	0.04 Gm.
Water q. s.	100 ml.

This medium was prepared by adding 73 grams of the dried material to two liters of distilled water. The solution was boiled for fifteen minutes and dispensed in flasks (200 ml. per flask), autoclaved at fifteen pounds and 250° F. for fifteen minutes, cooled, and then inoculated. Due to extreme changes in the outside temperature,

* This medium was obtained from Eli Lilly and Co., Indianapolis, Ind.

P. fragariae and *P. infestans* ceased to grow. Studies on these two organisms will be continued at a later date.

Testing of the Culture Filtrates

Culture filtrates, of the mediums listed above, from *P. cactorum* 6419 and 10091 and *P. fragariae* 10394 were tested by the paper disc method against the following organisms:

Bacillus subtilis
Staphylococcus aureus
Pseudomonas aeruginosa
Escherichia coli
Salmonella paratyphi A
Salmonella paratyphi B
Salmonella typhosa
Neiseria catarrhalis

Although the filtrates were concentrated to one-half and one-fourth their original volumes, at no time was antibacterial activity demonstrated.

Testing of Mycelium Proper

The freeze-dried mycelia of *P. cactorum* 6419 and 10091 and *P. fragariae* 10394 were tested by preparing sterile distilled water extracts at pH's 6, 7, and 8 in the following manner: Place five grams of the mycelium in a blendor and add 50 ml. of the distilled water at the specified pH and stir for fifteen minutes, filter the extract and test the filtrate by the paper disc method. All extracts although concentrated to one-half and one-fourth of the original volume showed no antibacterial activity.

The lyophilized mycelium of both species was subjected to serial extraction with solvents (petroleum ether, ether, acetone, chloroform, absolute alcohol and water) and the extracts were then reduced to dryness by freeze-drying and solutions were prepared by dissolving 10 mg. of the extract in 1 ml. of the solvent in question. (See Table I.) These extracts were used to make one-dimensional chromatograms which, in turn, were used for antibacterial screening. Five spots of thirty microliters each of a given solution were applied across the bottom of a sheet of filter paper (Whatman No. 1) one inch from the bottom of the sheet. Control chromatograms were run in the same manner except that the pure solvent used in making the extract and

TABLE I

SERIAL EXTRACTION OF MYCELIUM OF PHYTOPHTHORA CACTORUM

		Petroleum ether		Ether		Chloroform		Acetone		Absolute Alcohol		Distilled water	
	Weight of lyophilized Mycelia	Weight of Extract	% Extract	Weight of Extract	% Extract	Weight of Extract	% Extract	Weight of Extract	% Extract	Weight of Extract	% Extract	Weight of Extract	% Extract
PC10091	26.2gm.	.0576gm.	.28%	.2612gm.	.99%	.0879gm.	.335%	.179gm.	.68%	.156gm.	.595%	3.0875gm.	11.78%
PC6419	26.2gm.	.12gm.	.46%	.2127gm.	.81%	.038gm.	.145%	.041gm.	.16%	.1491gm.	.57%	5.436gm.	20.76%

the subsequent solution was substituted for the solution (Figure 1). These chromatograms were developed in sealed tanks at 25° C. with a developing liquid consisting of four parts n-butanol, one part of 95% ethanol, and one part of water. The development required four hours after which the chromatograms were air-dried for forty-eight hours and then tested for antibacterial activity against the organisms listed above, and in addition *Proteus vulgaris* and *Shigella dysenteriae* were added to the spectrum. The chromatographic sections divided as shown in Figure 1 were arranged on the seeded agar plates and incubated for eighteen hours at 37° C. The extracts (0.05 ml.) were also tested by the disc method.

Results

Testing the extracts obtained by solvents used serially by the disc method and by the use of strips of chromatograms indicated, in general, negative results. Slight inhibition of the growth of *Staphylococcus aureus* by the disc method was shown with the acetone, ethyl ether, chloroform, and water extracts of *P. cactorum* 6419 and with the ethyl ether and chloroform extracts of *P. cactorum* 10091; of the growth of *Bacillus subtilis* by the chloroform extract of *P. cactorum* 10091; and of the growth of *Salmonella paratyphi A* and *S. typhosa* by the water extract of *P. cactorum* 10091. However, these results were not confirmed by the tests using chromatogram strips. These results also confirm those of other workers (although their techniques were different) which indicates that the Phycomycetes have little or no antibacterial activity (8, 9). In some instances, however, there was evidence of the presence of growth accelerating substances. There were marked differences in the amount of material that was extracted by the solvents from the two strains of *Phytophthora cactorum* studied.

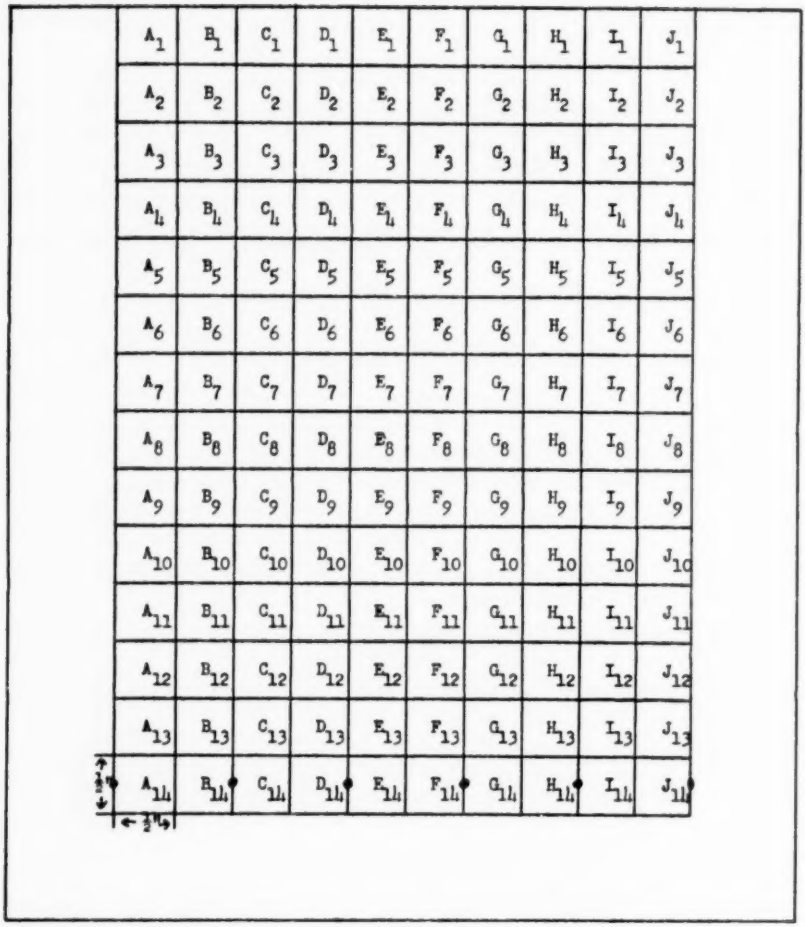

FIGURE 1

An example of a *Phytophthora cactorum* chromatogram which has been prepared for antibacterial testing. Since each vertical column is identical, the ten columns can be tested against ten different bacteria by using 1 column for each bacteria.

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THE REQUIREMENT FOR PROOF OF UTILITY IN PATENT APPLICATIONS FOR THERAPEUTIC PRODUCTS

By Leonard P. Prusak *

THE concept that the practice of pharmacy is restricted to the compounding of prescriptions has largely been discarded as absurd. Indeed, it would be fatal to adhere to a maxim which reflects nothing but sentiment and nostalgia. The relationship between the pharmaceutical profession and our basic economy has been forcefully demonstrated in the recent struggle for Fair Trade legislation. Prior to that was the well-publicized controversy over prescription refills, which was translated successfully into the Durham-Humphrey Act. Barbiturate legislation on the Federal level still remains an unsolved problem. The questionable practice of grocers and hawkers peddling pharmaceutical products is a present dilemma which must soon be resolved favorably if the highest standards of the profession are to be maintained.

Underlying all of these problems is the inalienable linkage between pharmacy and the law. Failure to appreciate this fundamental premise would be disastrous, for the existence of a profession and its related industry is necessarily dependent on its understanding and support of the American legal system. The protective benefits conferred upon pharmacy as a result of legislation on all governmental levels are too numerous to be recited here. Suffice it to say however, that the art of pharmacy could not have survived the dynamic revolution of the American economy were it not for the endowments bestowed upon it as a result of self-preserving legislation.

Paramount in this legislative ideology of preserving the rights of the sciences and professions is the influence of the American Patent System. With firm and indomitable purpose it has protected the property rights of inventors since the time of its inception. Of late years it has been particularly instrumental in preserving the interests of the American public by denying patent protection to fraudulent, deceitful, frivolous and useless inventions. Its impact in this

* Division 43, U. S. Patent Office, Washington, D. C.

respect has been singularly felt in the field of therapeutic products and processes, where the subject matter must be scrutinized meticulously not only to preclude the possibility of fraud upon the public, but also to ascertain the usefulness of the alleged invention to the degree stated in the disclosure.

There exists today, among the members of the pharmaceutical profession, the popular but misguided belief that all, or nearly all, of the medicinal compositions on the market have been accorded patent protection. Nothing could be farther from the truth. Although it cannot be denied that numerous therapeutic compositions and processes for their manufacture are protected under the Patent Laws, it does not necessarily follow that similar rights and privileges have been embraced by all manufacturers of medicinal products. Accordingly, it is the purpose of this paper to discuss the patentability of therapeutic compositions intended for the treatment or alleviation of diseases in human beings and, more particularly, the requirement for proof of utility therefor.

The requirement for proof of utility is not based on an administrative ruling. On the contrary, it stems directly from the Constitution, which vests the Congress of the United States with the "power to promote the Progress of Science and the Useful Arts, by securing for limited times to . . . Inventors the exclusive right to their respective . . . discoveries" (1). Congress has expressed its intent to exercise this power in the enactment of the Patent Statutes. In the Patent Act of 1952, which is the latest revision and codification of the laws relating to patents, the requirement for utility is specifically recited. Whoever invents or discovers any new and "useful" process . . . or composition of matter . . . may obtain a patent therefor (2). The specification shall contain a written description of the invention, and of the manner and process of making and "using" it, in such full, clear and concise and exact terms as to enable any person skilled in the art . . . to make and "use" the same (3).

All applications filed in the United States Patent Office wherein the subject matter is a mixture of ingredients or a process of treatment directed to the use of a specific compound and intended to be used in the prevention, cure or treatment of pathological conditions of the living body are classified in Class 167, otherwise known as "Medicines, Poisons and Cosmetics" (4). This class comprises oils, fats, alkaloids, organic and metallic compounds, glandular, tissue and animal extracts,

vaccines, antibiotics, sera, blood plasma expanders and similar biological and pharmaceutical compositions. The medicinal class is unique among all other classes of subject matter, in that all applications for patents placed thereunder recite an alleged usefulness in the treatment of human or animal diseases. As a result, the burden of proving such usefulness, otherwise known as "utility", rests entirely on the applicant. Irrespective of the fact that the prospective patentee is capable of meeting other statutory requirements such as inventiveness, novelty, complete disclosure, etc., the Examiner in charge of the application will not allow any of the claims unless utility is satisfactorily established.

Proof of therapeutic utility is largely a matter of degree. There is no fixed or prescribed rule on which the inventor can rely in order to meet the requirement successfully. Since each case necessarily stands on its own facts, it is difficult to set forth predetermined rules which could be adapted universally for purposes of meeting the requirement in all cases relating to medicinal compositions. Such considerations as the nature of the disease which the product is allegedly capable of treating and the character of the composition with respect to toxicity, reliability, effectiveness, etc., are variables which preclude definitive formulation. The Court of Customs and Patent Appeals in the case of In re Bremner (5) recognized the elasticity of the requirement, but remained adamant in demanding a disclosure of usefulness:

> "No hard and fast ruling properly may be made fixing the extent of the disclosure of utility necessary in the application, but we feel certain that the law requires that there be in the application an assertion of utility and an indication of the use or uses intended. It was never intended that a patent be granted on a product . . . unless such product be useful."

Although the Bremner decision does not specifically relate to proof of therapeutic utility, it does nevertheless express the current judicial attitude toward applicants who fail to recite positively the scope of the usefulness of their discovery.

The requirement for proof of utility in applications for medicinal products is not satisfied however, by the mere recitation that the product is useful in the treatment of certain diseases of the human body; nor is it sufficient to state simply that successful tests had been

carried out, thereby predicating usefulness of the product on the alleged tests. On the contrary, the therapeutic properties of the composition having been disclosed, it is then incumbent upon the applicant to submit evidence of utility commensurate with such disclosure.

In the case of Hoover v. Eckerd's, involving a patent infringement matter, the District Court of Delaware considered the merits of a dentifrice composition purportedly possessing the property of calcifying the teeth artificially (6). The plaintiff showed tests of calcification on extracted teeth. The soundness of the calcification theory was not recognized either in the art or by the public. The court, accepting the testimony of the defendant's expert witness that such tests were not in any way comparable with anything that takes place in the mouth, declared that a "calcifying dentifrice that will not calcify is inoperable and therefore not useful'. A similar holding was made in an infringement suit involving a synthetic composition commonly known as amphetamine sulfate (7). The New Jersey District Court stated:

> "It is the (useful) effect it produces which brings the composition up to the standard of invention in therapeutics. Without the useful effect, the composition, although new, is of no value, except possibly academically, and certainly unpatentable. The field of chemistry is filled with formulas and compositions for which no use has yet been found."

The Court of Customs and Patent Appeals, in In re Oberweger, considered the usefulness of a mixture of Cod Liver Oil. marrow and alcohol as a treatment for the human scalp (8). The Examiner had rejected all of the claims on the ground of lack of utility since compositions for growing hair on the human scalp have been uniformly proven unreliable. Affidavits of the inventor and a Doctor of Medicine did not convince the court that the composition was capable of restoring hair on bald heads:

> "Certainly there is nothing in this record to show that appellant's composition is any better than the many hundreds of similar concoctions that have been advertised and sold to a credulous public since the beginning of recorded history. It is a matter of common knowledge that numerous preparations, similar in many respects to the one at bar have been advertised and sold

for the purposes of producing hair on bald heads and which were totally lacking in utility, often harmful to the human body, and whose sale was generally understood to be a fraud upon the public."

The Board of Appeals of the United States Patent Office has consistently sustained Examiners in their requirement for a positive showing that new and untried medicinal compositions are in fact effective when administered to human beings. In the case of Ex parte Wolf (9) for example, the invention related to a process of isolating a renal extract which purportedly had blood pressure reducing properties, i.e., a hypotensive agent. The inventor presented evidence that his extract was capable of reducing blood pressure of guinea pigs and rats with experimental hypertension. The Examiner contended however, that by a "successful test" is meant the administration of a suitable dose to a human being having high blood pressure with observations of the person to determine the effects produced. The Board agreed fully with the Examiner on this point, stating that his was a "reasonable and proper conclusion".

In a case involving an allegedly effective therapeutic agent for "leukemia, carcinoma, obesity, gonadism and menopausal hypertension", the only proof submitted was in the form of a paper presented at a medical meeting which indicated that certain agents covered by the claims may have some beneficial effect in the treatment of leukemia. The Board stated:

"Patents on therapeutic agents are not granted on mere possibilities or on unsubstantiated theories, but there must be positive proof that the therapeutic agents do have the beneficial effect upon each and every disease to which they are stated to be applicable.

"The history of medicine is replete with instances where various medicinal preparations have been tried as a cure for various diseases which at first appeared to have possible beneficial effect upon such diseases, yet when tried on a sufficiently large number of cases have finally proven worthless" (10).

Despite the decisions handed down by Patent Office tribunals that proof of utility on animals is not equivalent to proof of the same order of utility in human beings, applicants persist in advancing the

argument that a particular pharmacologic response in lower animals is tantamount to an identical occurrence in human beings. No amount of experimental evidence nor any quanta of forensic persuasion has been sufficient to convince the Board of Appeals that such is actually the case. In a proceeding before the Board decided on June 17, 1952, the applicant alleged throughout her specification that her antigen was therapeutically effective when tested on experimental animals. The affidavits filed during the prosecution of the case however, included humans, showing an intent that the findings were intended to apply to both lower animals and humans. The Board stated:

> "Applicant by affidavit and argument has developed a record showing an intent to include among the utilities of the antigen . . . its use by humans. Hence it was incumbent upon applicant to submit evidence of the kind customarily presented where humans are involved" (11).

The problem of satisfactorily meeting the requirement is at times a very difficult one. This is especially true in the field of biological products such as vaccines. In such cases it is invariably urged that the requirement is not only unreasonable, but is opposed to the constitutional provision that Congress is to "promote" the progress of science. The argument is advanced that it is a formidable task to seek out clinicians who are willing to try the product under controlled conditions, and even though the services of such experts are eventually gained, the only tests to which human volunteers are willing to subject themselves are those relating to toxicity and tolerance. Moreover, it is argued, the procurement of volunteers who are willing to be challenged with a virulent microorganism is not only a needless undertaking, but such demands are arbitrary and unduly burdensome as prerequisites to patentability. Why, it is asked, are not animal experiments to be considered sufficient if they are shown to be statistically successful?

These arguments however, have been consistently rejected as untenable. As Shimkin (12) very aptly points out: "A primary scientific criterion of usefulness in drug research is whether the observed pharmacologic response can be produced in human beings. Findings on other species may have general validity for man, but the conclusive establishment of such validity must rest in each case upon direct observations on man. Since many disease processes have not

been fully reproduced in animals, medical investigation must necessarily include human beings. Abnormalities in animals are so difficult to find that no study except on human beings is conclusive. Thus, clinical experimentation on a group of volunteer cases, including adequate controls, is the only practicable method of collecting and evaluating data that would otherwise be dispersed and inaccessible". A recent appeal to the Patent Office Board of Appeals is a case in point (13). The appellant therein urged that he had adequately fulfilled the requirement for utility since he had identified and assayed his insulin composition on rabbits in strict compliance with the standards set forth in the United States Pharmacopeia. The Examiner held that experiments on rabbits do not constitute proof of utility on humans. The appellant contended that the rejection was arbitrary. The Board of Appeals stated in part:

> "It appears to us that when an applicant has presented no evidence in his application that his product may be safely used for medicinal purposes for human beings, the Examiner is unconvinced that it is a safe and effective product for such use, he may require the applicant to establish the utility of his product. A rule of extreme caution has arisen in the Patent Office in dealing with claimed therapeutic remedies. We find ourselves constrained to follow this rule, because we consider it salutary and in the interest of the public."

It is sometimes contended by applicants that the Patent Office is exceeding the scope of its administrative authority because Congress has established the Food & Drug Administration for the investigation of the efficacy of drugs and has provided punishment for those who deliver any drug not approved into interstate commerce. Since Congress has provided an agency which can adequately safeguard the public's interests, it is argued that no obligation rests on the Patent Office to require proof beyond a reasonable doubt as a prerequisite to the grant of a patent. This argument has been summarily rejected by the Board of Appeals:

> "We are of the opinion however, that the Patent Office is not relieved of the duty of examining the facts of each case on pharmaceuticals coming before it with a view of determining if there has been established utility within the field covered by the claims. . . . It appears to us that proofs of utility of com-

> positions which may be intended to be used for internal medication should be in accordance with the seriousness of the use contemplated" (14).

In an earlier decision involving a pharmaceutical composition allegedly possessing therapeutic properties, the Board succinctly stated:

> "It is our opinion that the evidence before us does not justify putting the stamp of approval of the Patent Office upon appellant's remedy" (15).

One of the most controversial fields of medical endeavor today is that of cancer research. Ever since the recognition of cancer in the early days of civilization efforts have been made to eradicate the disease (16). The tremendous financial burden imposed upon systematic research into this deadly and mysterious malady, and the necessity for early recognition of symptoms of cancer, has precipitated a large amount of publicity directed toward the familiarization of the general public with the nature of the disease. As a result, the advertisement and exploitation of so-called "cancer cures" has lead to the tragic dissolution of unwaranted hopes excited in the lay mind as a result of such announcements (17).

Applications for cancer remedies filed in the United States Patent Office are uniformly rejected "for lack of utility in the absence of clear and convincing evidence that the composition is safe, effective and reliable". It is then incumbent upon the inventor to present proof, in affidavit form, that his composition has been subjected to clinical trials, including controls, under skilled medical supervision by operators other than the proponent himself. Actual clinical cases are required, setting forth histologic diagnoses that the patients were in fact afflicted with cancer; conclusive and unequivocal proof that the malignancy was cured in all stages, even in the face of recurrences and generalized metastases; and an indication that the cure was permanent, as evidenced by follow-up examinations (18).

That this requirement is neither unreasonable nor arbitrary is amply evidenced by Board decisions (supra); nor is this attitude restricted to tribunals trying patent causes exclusively. In a recent case involving the Huxsey Cancer Clinic of Dallas, Texas the United States Court of Appeals considered the question of the value of lay testimony as to the merits of a cancer cure (19). The court not only

unanimously rejected such testimony as being without value, but laid down the dicta that the diagnosis of cancer requires biopsy and that surgery, X-Ray and radiation are the only known effective means for treating cancer. The court ruled:

> "Despite the vast and continuous research which has been conducted into the cause of and possible cure for, cancer, the aggregate of medical experience and qualified experts recognize in the treatment of internal cancer only the methods of surgery, X-Ray, radium and some of the radioactive by-products of atomic bomb production.
>
> ". . . the personal testimony of the lay sufferer is entitled to no weight . . . since . . . not even the experts can diagnose this condition without the aid of biopsy and pathological examination."

The medical profession, an assiduous and recognized crusader against unproven and untried therapeutic products, has bitterly denounced irresponsible endorsement of "cancer cures" and has encouraged government officials in guarding the public against overoptimism concerning such remedies. On August 9, 1952 the Journal of the American Medical Association editorialized:

> "Persons in high government office and other responsible positions also have an obligation to the public to refrain from promoting new and inadequately tested therapeutic measures. Such misguided activity can result in incalculable harm to the health of the public" (20).

Summary

The requirement for positive and unequivocal proof of therapeutic utility is a just and reasonable one. It stems directly from the United States Constitution and has, as one of its objectives, the preclusion of fraudulent, foolish and useless remedies bearing the stamp of approval of the Patent Office. On the basis of decisions of Patent Office tribunals and the judiciary, it is manifest that the Congress did not intend to clothe with patent protection untried and unproven therapeutic products intended for use on human beings. Thus, patents on medicinals are granted only upon submission of convincing proof that the alleged invention is capable of performing all of the phar-

macologic functions attributed to it in the specification. As to the nature of the proof, no specific kind is mandatory. Applicant is advised to supply what proof he can and if the proof submitted is not satisfactory he is fully advised in what respect it is deficient to prove the therapeutic allegations made. Where the composition does not have an accepted utility for humans, experiments on animals are not reliable indicia of therapeutic effectiveness in human beings. Thus the United States Patent Office is properly discharging its statutory function by granting patents only for such therapeutic compositions which meet the requirements for patentability as expressed in the Constitution, the patent statutes and the decisions of the judiciary.

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SELECTED ABSTRACTS

Vitamin A Cream in the Treatment of Dermatologic Conditions. Lubowe, I. I., *Am. Perfumer 61*:284 (1953). In a communication the author pointed out the value of including vitamin A in certain dermatological conditions and suggested three formulas which had proven satisfactory in his practice. He pointed out that vitamin A is essential in epidermal metabolism in order to prevent excessive metaplasia and hyperkeratosis. In acne, keratosis follicularis, xerosis, icthyosis, atopic eczema, seborrheic keratosis, keratosis pilaris, and glossitis it is felt that there is a lack of vitamin A.

The chief difficulties encountered in the incorporation of the vitamin in cosmetics are the stability of the vitamin, the odor, and the solubility. The use of synthetic vitamin A palmitate and the incorporation of glycol esters has helped to eliminate the latter two difficulties. Vitamin E has been included in some cases to improve the stability by acting as an antioxidant.

A formula suggested for an all-purpose cream is as follows:

Vitamin A	100,000 units
Sesame Oil	10.0 cc.
Duponol	1.0 Gm.
Hydrophilic Ointment U. S. P. q.s. ad	100.0 Gm.

A formula suggested for a vitamin A and D ointment is as follows:

Vitamin A	150,000 units
Vitamin D	50,000 units
Lanolin	10.0 Gm.
Oil of Rose	3.0 gtts
Hydrophilic Petrolatum q.s. ad	100.0 Gm.

The author stated that he had used vitamin A and D and cod liver oil ointments for a number of years in the treatment of fissures and ulcerations of the skin to produce rapid epithelialization, with excellent results.

The Use and Abuse of Ophthalmic Ointments. Dozier, H. B., and Renken, P. W. *South. Med. J. 45*:1071 (1952). The authors discuss the occasions on which ophthalmic ointments should be applied to the eye and when they should not. When employed properly they feel that ointments have a very important place in therapy, but in other circumstances they are definitely contraindicated.

Ointments should be applied at night to the eye of a patient with acute conjunctivitis and drops used during the day. They are also valuable for chronic conjunctivitis, blepharitis, styes, chalazia, or pediculosis ciliaris.

However, ointments should not be applied when the entire thickness of the corneal epithelium is broken by a deep ulceration or other lesion. The corneal epithelium will regenerate best if no agent whatsoever is used. When abrasions or lesions are present small globules of ointment may work their way under the epithelium and mechanically delay healing. When ointments contain anesthetics or sulfonamides the regeneration of the epithelium seems to be especially retarded. Although penicillin is more effective in ointment form than in solution and does not inhibit regeneration, the danger of the development of sensitivity has caused the authors to discontinue the use of penicillin ointment entirely.

The authors also pointed out that once an ointment tube is opened the danger of contamination is quite great, even though the ointment was sterile to begin with. Many active ingredients in ointments are in the form of small crystals. There is considerable danger that the sharp edges of these solids may abrade the cornea with a subsequent development of an ulcer.

Anesthetics should not be used in ointment form. When an anesthetic is applied a bandage is often considered to be unnecessary. However, bandaging does speed healing, perhaps because the temperature of the conjunctival sac is raised. If not bandaged and anesthetized, the insensitive and unprotected cornea is especially susceptible to injury. When severe pain is present a systemic analgesic and/or hypnotic is better.

The production of miosis or cycloplegia is better controlled with drops than with an ointment and is just as effective. Undesirable systemic toxic effects from potent drugs such as atropine, eserine and prostigmin are more easily controlled when the local application has been in the form of drops rather than an ointment.

The Effect of Non-Ionic Emulsifiers in the Basal Diet of Rats. Chow, B. F., Burnett, J. M., Ling, C. T., and Barrows, L. *J. Nutrition 49*:563 (1953). An attempt was made to evaluate the effect of non-ionic surface active agents when administered under controlled conditions in the diet of rats. This factor is important because of the increasing use of these agents in food preparations. A 5 per cent concentration of polyoxyethylene sorbitan monostearate (Tween 60) was added to a basal casein diet for weanling rats. Diarrhea developed and the growth rate was retarded in these rats.

In another series of weanling rats maintained on a soybean basal diet, levels of 5 per cent and of 15 per cent of Tween 60, sorbitan monostearate (Span 60), and polyoxyethylene monostearate (Myrj 52) were added to the diet. None of these rats developed diarrhea but the rats receiving 15 per cent Span 60 showed some retardation of growth. Further study indicated that at least part of the growth retardation in the latter case was due to a reduced food consumption.

The authors explained the difference between the effect obtained with the basal casein diet and the basal soybean diet on the fact that the basal casein diet is almost completely metabolized with very little fecal residue. With soybean this is not true. It was felt, therefore, that the greater fecal residue with the soybean diet provided a protective effect and prevented the surface active agent from exerting an irritating effect on the intestine.

At the end of 14 weeks of feeding on the prescribed diets the animals were sacrificed. No abnormal histological nor pathological changes were observed in the animals maintained on either the 5 or 15 per cent levels of surface active agents.

A series of older rats were also fed the basal soybean diet with 5 per cent Tween 60 for a period of 14 weeks. No loss of weight nor development of diarrhea occurred in any of these rats.

Thus, the authors concluded that under the conditions of these tests no observable toxic effects occurred from these three non-ionic surface active agents.

The Treatment of Thyrotoxicosis With Neo Mercazole. Doniach, D. *The Lancet I*:873 (1953). The new anti-thyroid compound Neo Mercazole (2-carbethoxythio-1-methylglyoxaline) was used in the treatment of 90 cases of thyrotoxicosis and in the prepara-

tion of 30 other such cases for operation. Neo Mercazole is a modification of 1-methyl-2-mercaptoimidazole (Tapazole) in which the H of the thio group is replaced by a carbethoxy group. It is thought that this new compound is hydrolyzed to Tapazole in the body before it exerts its anti-thyroid action. Comparative studies have shown that the Neo Mercazole gives greater therapeutic efficiency, and it is felt that this is probably due to the maintenance of a steadier blood level produced by the slow release of Tapazole.

In the 120 cases treated in this study the initial daily dose of Neo Mercazole was 15, 30 or 45 mg. depending on whether the condition of the patient was considered to be mild, average or severe. As soon as the patient became euthyroid the dose was reduced as far as possible to maintain the improvement of the patient. Of the 120 patients 93 became euthyroid within 2 to 8 weeks. The remaining 27 patients responded less rapidly. Nine were operated on and the rest were controlled in 3 to 6 months. Goitrogenic reactions were avoided by carefully controlling the maintenance dose.

No toxic reactions were observed even though in many cases 30 mg. a day were given. Previous reports regarding Tapazole have indicated that 30 mg. a day almost invariably produced toxic reactions. On a calculated basis 30 mg. of Neo Mercazole contains only 18.5 mg. of Tapazole. This probably accounts for the reduced toxicity. However, weight for weight, Neo Mercazole appears to be at least as effective clinically as Tapazole. The final remission-rate, toxicity evaluation, and effectiveness of treatment will require more prolonged observation of the patients in this series as well as studies involving a greater number of patients.

BOOK REVIEW

Fisher—Frerichs—Awe; Lehrbuch der Chemie für Pharmazeuten, Lebensmittel—Chemiker, Mediziner und Biologen. By Professor Dr. Walther Awe, Technische Hochschule, Braunschweig. Tenth completely revised and enlarged edition. 2 Volumes. In 8 instalments. First and second instalment. 128 pp. each. $4.00 (approximately) each instalment. Paperbound. Publisher: F. Enke, Stuttgart.

The last edition of this textbook which is rather popular in the German speaking countries appeared in 1938. This new edition is in the process of publication and will appear in eight paper bound instalments of 128 pages each. When the work is finished, the first three instalments will comprise the first volume, General and Inorganic Chemistry—and the following five instalments the second volume—Organic Chemistry. The reviewer has received the first two instalments which appeared in 1952. Though a final evaluation cannot be rendered before the work is complete it can be stated that in the first two instalments Professor Awe has performed his task thoroughly and skillfully. Since the last edition was published, 15 years have passed and during this interval science has progressed rapidly. That brought about the complete rewriting of many chapters, i.e., those dealing with general chemistry—nuclear fission, isotopes, and radio-activity, to name just a few. The latter topics are presented in a particularly concise and clear fashion.

The first instalment is devoted almost entirely to general chemistry—structure of matter. In addition the first two chapters of inorganic chemistry are presented—hydrogen, oxygen and water.

Continuing the discussions of inorganic chemistry, the second instalment deals with the non-metallic elements. Silicon is the last chapter.

It must be emphasized that this text also includes the tests and assays as required by the German Pharmacopoeia. It is therefore the textbook of choice for the pharmacy student in chemistry.

The tenth edition marks another milestone in clear, concise writing on a complex subject.

E. Ehrenstein

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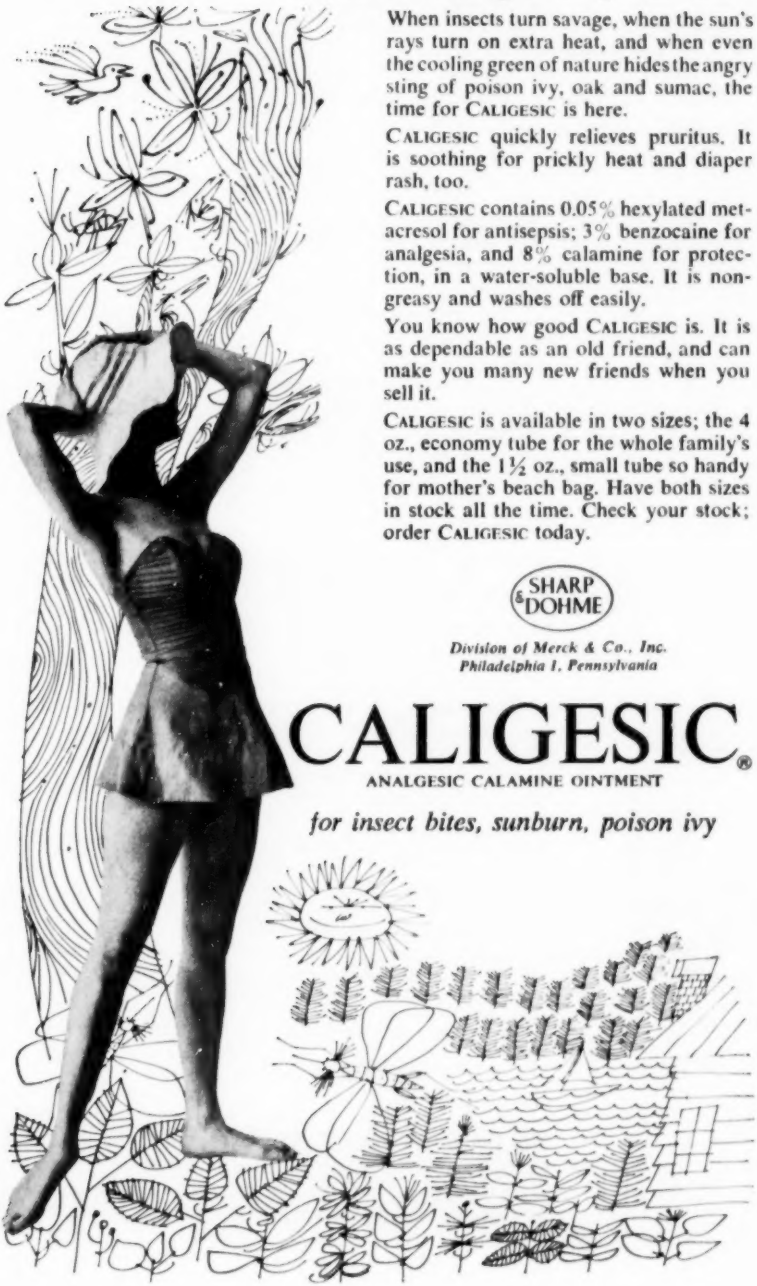

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